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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,496	06/22/2001	Partha S. Banerjee	18025-1014	7707

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FROMMER LAWRENCE & HAUG
745 FIFTH AVENUE- 10TH FL.
NEW YORK, NY 10151

EXAMINER	
KANTAMNENI, SHOBHA	
ART UNIT	PAPER NUMBER
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/887,496	BANERJEE ET AL.	
	Examiner	Art Unit	
	Shobha Kantamneni	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-21,23-38,40-64,69-76,78-83,87-89,93 and 99-122* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *1, 3-21, 23-38, 40-64, 69-76, 78-83, 87-89, 93, 99-122* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 01/05/2007, wherein claims 5, 87-89 have been amended.

Applicant's amendment by deleting the recitation "prevention" is sufficient to overcome the rejection of claims 87-89 under 35 U.S.C. 112, first paragraph, for scope of enablement. The rejection is herein withdrawn.

Applicant's arguments have been fully considered, but not found persuasive, and the rejection of claims 1, 3-21, 23-38, 40-64, 73-76, 78-83, 87-89, 99-112, 117-119, and 122 under 35 U.S.C. 103(a) as being unpatentable over Hochrainner et al. (US 6,150,418, PTO-892 of record) in view of Blondino et al. (US 6,004,537, PTO-892 of record) or Carling et al. (US 5674860, PTO-892 of record) is MAINTAINED. See under response to arguments.

Applicant's arguments have been fully considered, but not found persuasive, and the rejection of claims 69-72 under 35 U.S.C. 103(a) as being unpatentable over Hochrainner et al. (US 6150418, PTO-892 of record) in view of Carling et al. (US 5674860, PTO-892 of record) or Blondino et al. as applied to claims 1, 3-21, 23-38, 40-64, 73-76, 78-83, 87-89, 99-112,117-119, and 122 and further in view of PDR is MAINTAINED.

Applicant's arguments have been fully considered, but not found persuasive, and the rejection of claim 93 under 35 U.S.C. 103(a) as being unpatentable over Hochrainner et al. (US 6150418, PTO-892 of record) in view of Blondino et al. (US 6004537, PTO-892 of record) or Carling et al. (US 5674860,

PTO-892 of record), and further in view of PDR at pages 482, 535, 537, 2828 (of record) is MAINTAINED.

Applicant's arguments have been fully considered, but not found persuasive, and the rejection of claims 113-116 and 120-121 under 35 U.S.C. 103(a) as being unpatentable over Hochrainner et al. (US 6150418, PTO-892 of record) in view of Blondino et al. (US 6004537, PTO-892 of record) or Carling et al. (US 5674860, PTO-892 of record), and further in view of Hardman et al. (Goodman Gilman 's *The Pharmacological Basis of Therapeutics*,1996, page 665, of record) or Leckie et al (*Novel Therapy* Of COPD, abstract, Jan 2000, of record) is MAINTAINED.

Claims 1, 3-21, 23-38, 40-64, 69-76, 78-83, 87-89, 93 and 99-122 are pending.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-21, 23-38, 40-64, 73-76, 78-83, 87-89, 99-112, 117-119, and 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hochrainner et al. (US 6,150,418, PTO-892 of record) in view of Blondino et al. (US

6,004,537, PTO-892 of record) or Carling et al. (US 5674860, PTO-892 of record).

Hochrainner et al. discloses propellant-free pharmaceutical composition comprising formoterol particularly stable on storage with concentration 10 –500 mg/ml (see col.1 line 65-67; col.2 line 6-11), in aqueous ethanol, and ethanol mixture (water and ethanol are well known polar and protic solvents, see col.2 lines 24-34), in the form of a solution or suspension for use in inhalers for nasal therapy, see abstract and claims 1-4 in particular. Hochrainer et al. further teaches that the pharmaceutical composition is such that it can be administered by inhalation using a suitable nebuliser, see col.4, lines 19-20 and col. 5, lines 33-41. Hochrainer et al. teaches that the pH range is preferably between 2.0-7.0 and most preferably between 4.5-5.5. The employment of inorganic acids and organic acids such as phosphoric acids, citric acid and the employment of buffers in its composition are also taught, see in particular col.3, lines 35-40 and col.4 line 55 to col. 5, line 7; and inorganic salts, sodium chloride, and organic salts such as for example, sodium, potassium or ammonium salts of citric acid (see col.2 lines 56-64) in the composition is also taught. Hochrainer et al. teaches the concentration of formoterol to be between about 75 mg/ml and about 500 mg/ml, which may be used with diluent, and other ingredients for the preparation of therapeutical composition. See in particular claims 1-4. Hochrainer et al. also teaches that additional active ingredients such as steroids, antichlolinergics could be incorporated in its composition, see claim 19. It is taught that the formulation for administration is obtained by diluting to 0.9 mg/ml of formoterol with the

diluents such as water, aqueous saline and the PH is adjusted for stable storage. See column 4, lines 26-29; column 5, lines 1-6. Hochrainer et al. also discloses a kit or an article of manufacture comprising the same combination and a nebulizer. See column 5, lines 33-47. The compositions therein are employed in the methods of treating obstructive respiratory diseases and asthma, see col. 1, lines 1- 37. A formulation containing a solvent mixture of ethanol/water, formoterol in a concentration of about 0.9 to about 1.5 mg/ml adjusted to a pH of about 4.5 to about 5.5 is also disclosed. See column 8, claim 22.

Hochrainer et al. does not teach particularly the employment of a steroidal anti-inflammatory agent, budesonide or fluticasone propionate.

Hochrainer et al. does not explicitly teach the concentration of formoterol such as 50 μg/ml to about 200 μg/ml, 59 μg/ml, 118 μg/ml in its pharmaceutical composition, and does not expressly teach the concentration of buffer providing particular PH value, and the ionic strength of the composition.

Blondino et al. discloses a pharmaceutical composition comprising formoterol (free base) or formoterol fumarate salt in combination with the specific steroid anti-inflammatory agent, budesonide (see col.2 lines 9-25), in a pharmaceutically acceptable carrier such as a liquid, co-solvents of alcohols such as ethanol or isopropanol (see col.2 line 55-59), by inhalation from a nebulizer for treatment (see title and abstract, claims 1-30). Blondino et al. also discloses the effective amounts of formoterol, in amount 0.01-0.5% by weight in a pharmaceutical composition therein (see claim 1). Blondino et al. also discloses that the composition or formulation therein is stable under elevated temperatures,

e.g., 45^{0}C (see col.2 lines 35-37). Blondino et al. also discloses that a pharmaceutical composition of the combination therein is formulated into a single dosage administration (see Example 1-4 at col.4). Blondino et al. also discloses a kit or an article of manufacture comprising the same combination and a inhaler (see col.3-4, claims 1-30).

Carling et al. discloses a pharmaceutical composition comprising formoterol (free base) or formoterol fumarate salt in combination with the specific steroid anti-inflammatory agent, budesonide, in a pharmaceutically acceptable fluid such as a liquid (see col.4 line 2), by inhalation from a nebulizer (see col.3 line 51) for the treatment of respiratory disorders such as asthma (see title and abstract, col.1 lines 10-15, 46-67). Carling et al. also discloses the effective amount of formoterol, 6-100 μg, preferred 6-48 μg (the instant claimed amount within the range of Carling et al.), in a pharmaceutical composition therein (see col.3 lines 44-45). Carling et al. also discloses that a pharmaceutical composition of the combination therein is formulated into a single dosage administration (see Example 1-3 at col.4). Carling et al. also discloses a kit or an article of manufacture comprising the same combination and a nebulizer (see col.3 line 8-10 and 50-52, claims 1-36). Carling et al. also discloses the employment of a tonicity adjusting agent herein such as salts of inorganic or organic salts, e.g., succinate, lactate (see col.3 lines 30-38) and adding oleic acid may improve the physical stability (see col.4 line 12-14).

From the teaching of Carling et al. or Blondino et al., it would have been obvious to one of ordinary skill in the art at the time the invention was made to

employ budesonide in the composition of Hochrainer et al. It is prima facie obvious to combine two agents which are known to be useful to treat asthma individually into a single composition useful for the very same purpose. See *In re Kerkhoven* 205 USPQ 1069.

It would have been obvious to a person of ordinary skill in the art at the time of invention to optimize parameters such as the concentration of formoterol in its pharmaceutical composition, and the concentration of buffer providing particular PH value, and the ionic strength of the composition. The optimization of a result effective parameter, e.g., the effective amounts of active ingredients and excipients in a therapeutical dosage form, is considered within the skill of the artisan. See, In re Boesch and Slanev (CCPA) 204 USPQ 215.

With regard to the limitations "whereby the composition has an estimated shelf-life of greater than 1 month usage time at 25 °C and greater than or equal to 1 year storage time at 5 °C, and "the composition is formulated for direct administration", Hochrainer et al. disclose a formulation containing a solvent mixture of ethanol/water, formoterol in a concentration of about 0.9 to about 1.5 mg/ml adjusted to a pH of about 4.5 to about 5.5, and further teaches that the compositions therein are obtained by diluting with polar solvents such as water, aqueous saline and adjusting the PH to obtain a stable formulation. See column 8, claim 22. Hochrainer et al. particularly teach that the concentrated solution may be used for making pharmaceutical composition which is such that it can be administered by inhalation using a suitable nebuliser, see col. 4, lines 19-20 and col. 5, lines 33-41. The compositions therein can contain steroids. Thus, absent

showing unexpected, and significant benefit residing in the particular limitation herein, the claimed invention would have been obvious to one of skill in the art.

Claims 69-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hochrainner et al. (US 6150418, PTO-892 of record) in view of Carling et al. (US 5674860, PTO-892 of record) or Blondino et al. as applied to claims 1, 3-21, 23-38, 40-64, 73-76, 78-83, 87-89, 99-112,117-119, and 122 and further in view of PDR.

Hochrainner et al., Carling et al. and Blondino et al. are as discussed above.

The prior art combination of references does not teach particularly the employment of a steroidal anti-inflammatory agent, fluticasone propionate or its concentration.

PDR teaches fluticasone propionate as a known corticosteroid readily employed in the method of treating asthma.

From the teaching of PDR, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ fluticasone propionate in the composition of Hochrainer et al. It is prima facie obvious to combine two agents which are known to be useful to treat asthma individually into a single composition useful for the very same purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069.

The optimization of a result effective parameter, e.g., the effective amounts of active ingredients and excipients in a therapeutical dosage form, is

considered within the skill of the artisan. See, In re Boesch and Slanev (CCPA) 204 USPQ 215.

Claim 93 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hochrainner et al. (US 6150418, PTO-892 of record) in view of Blondino et al. (US 6004537, PTO-892 of record) or Carling et al. (US 5674860, PTO-892 of record), and further in view of PDR at pages 482, 535, 537, 2828 (of record).

The same disclosures of Hochrainner et al. in view Carling et al. (US 5674860) or Blondino et al. have been discussed in the 103(a) rejection set forth above.

Hochrainner et al., Carling et al. and Blondino et al. do not expressly disclose further adding one or more agent recited in claim 93 herein to the composition.

PDR teaches that albuterol (beta2-adrenoreceptor agonist), accolate (leukotriene receptor antagonist) and Zyflo (5-lipoxygenase inhibitor) are all known to be effective in treating asthma.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ a third active such as those enumerated immediately above in a combination composition along with formoterol and budesonide.

One of ordinary skill in the art would have been motivated to employ a third active such as those enumerated immediately above in a combination composition along with formoterol and budesonide because all three actives are

known to be useful in treating asthma. Combining two agents which are known to be useful to treat asthma individually into a single composition useful for the very same purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069.

Claims 113-116 and 120-121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hochrainner et al. (US 6150418, PTO-892 of record) in view of Blondino et al. (US 6004537, PTO-892 of record) or Carling et al. (US 5674860, PTO-892 of record), and further in view of Hardman et al. (Goodman Gilman 's *The Pharmacological Basis of Therapeutics*,1996, page 665, of record) or Leckie et al (*Novel Therapy* Of COPD, abstract, Jan 2000, of record).

The same disclosures of Hochrainner et al. in view Carling et al. (US 5674860) or Blondino et al. have been discussed in the 103(a) rejection set forth above.

Hochrainner et al., Carling et al. and Blodino et al. do not expressly disclose further adding an anticholinergic agent such as ipratropium bromide or tiotropium bromide to the composition therein.

Hardman et al. teaches that ipratropium bromide is an anticholinergic agent useful in treating asthma.

Leckie et al teaches that tiotropium is a known bronchodilator employed in treatment of asthma.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ a third active such as ipratropium bromide or

tiotropium bromide in a combination composition along with formoterol and budesonide.

One of ordinary skill in the art would have been motivated to employ a third active such as ipratropium bromide or tiotropium bromide in a combination composition along with formoterol and budesonide because all three actives are known to be useful in treating asthma. Combining two agents which are known to be useful to treat asthma individually into a single composition useful for the very snme purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Note that applicant's arguments have been considered, but not found persuasive in view of the new ground(s) of rejections made in this office action, and as discussed below.

Applicant argues that "Hochrainer et al. also specifically teaches that its diluted compositions for direct administration are not stable." This argument has been considered, but not found persuasive because Hochrainer et al. teaches a stable formulation containing a solvent mixture of ethanol/water, formoterol in a concentration of about 0.9 to about 1.5 mg/ml adjusted to a pH of about 4.5 to about 5.5. See column 8, claim 22. The concentration of formoterol taught by Hochrainer et al. overlaps with the instantly claimed concentration i.e 5 μg/mL to about 2 mg/mL, and thus the formulation taught by Hochrainer et al. is deemed to have the same stability as instantly claimed.

Response to Arguments

Applicant argues that "the state of the art was that it was expected that an aqueous solution would hydrolyze formoterol and as such use of aqueous solutions was not thought to be a viable option for formoterol and as such use of aqueous solutions was not thought to be a viable option for formoterol containing compositions with expectations of long-term stability as claimed by the applicants. This is illustrated not only within the Hochrainer reference itself but in other references." This argument has been fully considered, but not found persuasive because Hochrainner et al. discloses propellant-free pharmaceutical composition comprising formoterol particularly stable on storage with concentration 10 –500 mg/ml (see col.1 line 65-67; col.2 line 6-11), in aqueous ethanol, and ethanol mixture (water and ethanol are well known polar and protic solvents. It is also disclosed that the aqueous composition comprising formoterol can be stored for a period from several months to several years. See column 1, lines 58-61. Thus, the aqueous solutions taught by Hochrainner et al. are stable for long-term storage.

Applicant argues that "supporting the obviousness rejection based on optimization of ranges (MPEP 2144.05 (section I) also requires that the particular parameters must first be recognized as a result-effective variable. However, there is no direction from any of the references or from within the state of the art that the formoterol concentration was a results effective variable and certainly not in the context of combination with aqueous solutions." This argument has been considered, but not found persuasive because Hochrainner teaches that the formulation for administration is obtained by diluting to 0.9 mg/ml of formoterol

with the diluents such as water, aqueous saline and the PH is adjusted for stable storage. Thus, there is clear direction from Hochrainer et al. reference that formoterol concentration was a results effective variable for obtaining desired therapeutic effect.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period, will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Tuesday, Thursday-Friday, 8am-4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shobha Kantamneni,Ph.D
Patent Examiner
Art Unit 1617

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER